Package Insert

TheraSphere® Yttrium-90 Glass Microspheres

Humanitarian Device.
Authorized by Federal Law for use in the radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training and experience.

DESCRIPTION

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass [1]. The mean sphere diameter ranges from 20 to 30 μm. Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3 mL vee-bottom vial secured within a 12 mm clear acrylic vial shield. A pre-assembled single use administration set is provided with each dose. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi) and 20 GBq (540 mCi).

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV.

Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect [2-6]. The spheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The spheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue [7-14].

INDICATION

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters.

CONTRAINDICATIONS

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 MAA hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques (see Item 1 under **INDIVIDUALIZATION OF TREATMENT**);
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under **INDIVIDUALIZATION OF TREATMENT**);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis; and

- who have severe liver dysfunction or pulmonary insufficiency.

PRECAUTIONS/WARNINGS

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Adequate shielding and precautions for handling radioactive material must be maintained.
- As in the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient extraneous to the therapeutic objective and to insure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.
- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The vial should always be stored in a shielded location away from personnel.

ADVERSE REACTIONS

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Adverse events that occurred in the 100 Gy HCC (N=22), the Pilot HCC (N=9) [4], and the Mixed Neoplasia (N=4) [3, 11] studies are summarized by severity in Table 1.

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract can cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99 MAA into the hepatic artery [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. The use of this product leads to irradiation of both tumorous and normal liver parenchyma. As a result patients with diseases which compromise the functioning of the non-tumorous liver parenchyma or with very small lesions scattered throughout the normal parenchyma may be at greater risk of liver function impairment.

Table 1
Incidence[a] of Treatment-Emergent Adverse Events From Three Studies[b] (N=35), SWOG Toxicity Grading System

Adverse Event	Mild	Moderate	Severe	Life Threatening	Lethal/Fatal	Total
Increased Transaminase (SGOT/SGPT)[c]	14 (40.0%)	15 (42.9%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	34 (97.1%)
Increased Alkaline Phosphatase	18 (51.4%)	9 (25.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	30 (85.7%)
Increased Lactic Dehydrogenase	19 (54.3%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	24 (68.6%)
Increased Bilirubin	0 (0.0%)	8 (22.9%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	19 (54.3%)
Abdominal Pain	6 (17.1%)	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
Decreased Hemoglobin	8 (22.9%)	4 (11.4%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	15 (42.9%)
Nausea	9 (25.7%)	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	13 (37.1%)
Anorexia	11 (31.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Other Pain[d]	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Decreased White Blood Cell	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Malaise/Fatigue/Lethargy	5 (14.3%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Fever, Absence Infection	4 (11.4%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.7%)
Increased Creatinine	6 (17.1%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Increased Prothrombin Time	5 (14.3%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Edema	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	7 (20.0%)
Weight Gain	5 (14.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
Gastric Ulcer	1 (2.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Other Liver[d]	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Vomiting	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
Anxiety/Depression	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Hemorrhage (Clinical)	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Other Gastrointestinal[d]	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Decreased Platelet	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Cough	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Dyspnea	0 (0.0%)	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Insomnia	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Weight Loss	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Constipation	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Diarrhea	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Hyponatremia	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Pneumonia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	3 (8.6%)
Sweats	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Dysrhythmia	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
Headache	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
Infection	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)

Abbreviations: SWOG, Southwest Oncology Group; HCC, hepatocellular carcinoma; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a] For each patient, the highest severity of an adverse event was counted once. Adverse events that were reported by at least two patients in the total population are summarized.

[b] Studies: 100 Gy HCC (N=22), Pilot HCC (N=9), and Mixed Neoplasia (N=4).

[c] If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

[d] Other pain included pain in back/lower back (3), epigastric (2), chest (1), legs (1), shoulder (1), stomach (1), toe (1), and musculoskeletal (1). Other liver included hepatitis (2) and ascites (4). Other gastrointestinal included abdominal discomfort (1), early satiety (1), heartburn (1), duodenal ulcer (1), and burping (1).

CLINICAL STUDIES

1. 100 Gy HCC Study

- *Objectives:* To define the activity of yttrium-90 microspheres given by hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma (HCC); to evaluate the survival of patients treated with yttrium-90 microspheres; and to evaluate the toxicity of yttrium-90 microsphere therapy.
- *Study Design:* Patients with HCC were treated with a target dose of TheraSphere® of 100 Gy by injection through the hepatic artery. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds or computerized tomography (CT) scans for up to 2 years after treatment. Response duration was calculated from the

date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading system (last revised 12/94), i.e., grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and grade 5 = lethal/fatal. If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

- *Patient Inclusion Criteria:* Presence of histologically confirmed unresectable HCC confined to the liver and at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0-3; estimated life expectancy greater than 12 weeks; absolute granulocyte count 2.0 x 10^8/L or greater; platelet count 100 x 10^9/L or greater; prothrombin time (PT) and activated partial thromboplastin time within normal limits; bilirubin less than 1.5 x upper normal limit; serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase less than 5 x upper normal limit; normal pulmonary function defined as no more than 30% greater or less than the expected normal.
- *Study Population and Treatment Administration:* Twenty-two patients were treated. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion. Nine patients were classified as Okuda stage I and 11 patients as Okuda stage II. The median activity administered was 3.9 GBq (range, 2.0 GBq to 9.2 GBq). The median liver dose was 104 Gy (range, 46 Gy to 145 Gy).
- *Safety Results:* One patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). Liver toxicities were primarily elevated enzymes during the week after treatment. The gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Three patients died during the follow-up period. The deaths were attributed to hepatitis (death approximately 5 months after TheraSphere® treatment; judged as possibly related to TheraSphere®), gastric ulcer (death approximately 2 months after TheraSphere® treatment; judged as probably related to TheraSphere®), and radiation pneumonitis (death approximately 2 months after TheraSphere® treatment; judged as definitely related to TheraSphere® after the patient received an estimated dose of 56 Gy to the lungs as a result of pulmonary shunting).
- *Probable Benefit:* As of February 14, 1997, only two patients remained alive resulting in a median survival of 378 days (95% CI, 209 - 719), with a minimum survival of 49 days and a maximum survival of 1265 days. Based on a stratified Cox survival analysis model; activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect.

2. Pilot HCC [4] and Mixed Neoplasia Studies [3, 11]

- *Objectives:* The objectives of the Pilot HCC study were to define the activity of yttrium-90 microspheres administered by hepatic arterial infusion to patients with HCC and to evaluate the toxicity of yttrium-90 microsphere therapy.
  The objectives of the Mixed Neoplasia study were to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion

that would be suitable for Phase II-III studies in a similar patient population.

- *Study Design:* Patients in the Pilot HCC study received TheraSphere® in an amount that was determined to deliver a radiation absorbed dose of approximately 50 Gy to the tumor. The Mixed Neoplasia study was designed to treat patients with metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobilliary carcinoma. Patients received a single injection of TheraSphere® with an initial group of patients receiving a calculated radiation absorbed dose of 50 Gy to the liver; after determination of acceptable and reversible toxicity, a second group of patients received 75 Gy to the liver followed by a third group of patients who received 100 Gy to the liver.

For both studies, response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the SWOG grading system (see above under 100 Gy HCC Study).

- *Study Population and Treatment Administration:* Thirteen patients, nine from the Pilot HCC study and four from the Mixed Neoplasia study, provide safety data. All 13 patients were treated once with TheraSphere®. The median activity administered was 2.6 GBq (range, 2.2 GBq to 6.6 GBq). The median liver dose was 74 Gy (range, 34 Gy to 105 Gy). Because of the dose escalation, seven patients received less than 80 Gy.
- *Safety Results:* All 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (43%). Liver toxicities were primarily due to elevated enzymes during the week after treatment. Among the serious adverse events, two patients also experienced gastric ulcers. Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).

- **Table 2. Therasphere® Median Survival (months)**

	Dose < 80 Gy	Dose ≥ 80 Gy
Adenocarcinoma	**9.1 (n=22)**	**9.7 (n=50)**
Hepatocellular	**3.6 (n=8)**	**11.1 (n=7)**

INDIVIDUALIZATION OF TREATMENT

1. Gastroduodenal ulceration is a potential complication of inadvertent disposition of radioactive microspheres. It is likely that inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain.
2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathologic abnormalities of the liver. For such patients, a fraction F of spheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product of the bypass fraction, F, and

the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This can be done by injecting a tracer dose of Tc-99 MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs [22]. Based on clinical study experience [15, 16] with radioactive microspheres and TheraSphere® in HCC treatment, an upper limit of F x A of 610 MBq (16.5 mCi) is recommended. The estimated dose (Gy) to the lungs is equal to A (GBq) x F x 50, and assuming the total mass of both lungs to be 1 kg [23]; an upper limit of dose to the lungs from a single TheraSphere® treatment is 30 Gy.

INSTRUCTIONS FOR USE

Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 3.

Table 2
Yttrium-90 Physical Decay Table
Half-Life 64.2 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	26	0.755	56	0.546
-2	1.022	28	0.739	58	0.534
0*	1.000	30	0.723	60	0.523
2	0.979	32	0.708	62	0.511
4	0.958	34	0.692	64	0.500
6	0.937	36	0.677	66	0.489
8	0.917	38	0.663	68	0.479
10	0.897	40	0.649	70	0.469
12	0.878	42	0.635	72 (Day 3)	0.459
14	0.859	44	0.622	96 (Day 4)	0.354
16	0.841	46	0.609	120 (Day 5)	0.273
18	0.823	48 (Day 2)	0.596	144 (Day 6)	0.210
20	0.806	50	0.583	168 (Day 7)	0.162
22	0.789	52	0.570		
24 (Day 1)	0.772	54	0.558		

*Calibration Time

Preliminary Patient Evaluation

Prior to the administration of TheraSphere® the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [21]. Following the placement of the hepatic catheter 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99 MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs. Air contrast scintigraphic views of the stomach are also obtained to confirm the absence of gastric and duodenal flow. If such flow is present and cannot be corrected using established angiographic techniques the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® can be administered.

Calculation of Dose

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Liver Mass (Kg)}]}{50\,[1-F]},$$

where F is the fraction of injected activity deposited into the lungs as measured by Tc-99 MAA.

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

If F is unknown, assume the upper limit of activity, which is 0.61 GBq, will be delivered to the lungs for the purpose of requisitioning TheraSphere®, and then using the Yttrium-90 Physical Decay Table (Table 3) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$\text{Dose (Gy)} = 50 \frac{[\text{Injected Activity (GBq)}]\,[1 - F]}{\text{Liver Mass (Kg)}}$$

The upper limit of injected activity shunted to the lungs is F x A = 0.61 GBq.

TheraSphere® Administration Set

The TheraSphere® Administration Set (Table 4 and Diagram 1) consists of one dose vial inlet set, one dose vial outlet set and one empty vial. Both the inlet set and the outlet set are made up of preassembled sterile, apyrogenic components as shown in the schematic diagram.

The dose vial inlet set, used to connect the fluid source to the TheraSphere® dose vial, consists of a fluid line (3), an inlet line (7) and a 5 mL pumping syringe (6), joined together via a red 3-way stopcock (4). The red stopcock is used to switch from the fluid line to the inlet line, so that fluid may be drawn into the syringe, then pumped through the inlet line and into the TheraSphere® dose vial.

The piercing pin (2) at the free end of the fluid line is used to connect the inlet set to the fluid source (1), usually a heparinized (100 U/mL) saline solution. The 20-gauge needle (9) at the free end of the inlet line is used to connect the inlet set to the TheraSphere® dose vial (10). A check valve (8) prevents spheres from flowing back into the inlet line. Consequently, the inlet set should not contain any radioactivity during a normal procedure.

The dose vial outlet set, used to connect the TheraSphere® dose vial to the patient catheter, consists of an outlet line (13) and a vent line (17) joined together via a blue 3-way stopcock (14). The patient catheter is connected to the free port (15) on the blue stopcock. The blue stopcock is used to switch from the vent line to the catheter (16), so that the system's lines can be properly vented before the TheraSphere® dose is administered. The 20-gauge needle (12) at the free end of the outlet line is used to connect the outlet set to the TheraSphere® dose vial. The dispensing pin and filter vent assembly (18) at the end of the vent line is used to connect the outlet set to the sterile empty vial (19). The empty vial is used to collect fluid and any spheres that may flush through during air venting. The filter vent in the dispensing pin prevents pressure buildup in the empty vial and also blocks any spheres from escaping. The dose vial outlet set, including the empty vial, may contain radioactivity at the end of the administration procedure. For added safety, the lead pot (20) used for shipping may be used to hold the empty vial during the procedure.

Throughout the administration procedure, the TheraSphere® dose vial (10) remains sealed within the clear acrylic vial shield (11) in which it was supplied. A removable plug at the top of the vial shield provides access to the septum of the TheraSphere® dose vial.

Administration Instructions

The entire contents of the TheraSphere® dose vial are administered to the patient.

The directions for administration should be followed to ensure accurate delivery of the calculated dose. Approximately 96% of the radioactivity in the TheraSphere® dose vial will be delivered to the patient using the recommended technique.

Assembly of Dose Vial Inlet Set (Table 4 and Diagram 1)

1. The fluid line (3) is connected to the fluid source (1) via the white piercing pin (2).
2. The 5 mL syringe (6) is connected to the free port (5) on the red 3-way stopcock (4).
3. The red stopcock is switched to the fluid line.
4. 5 mL of solution is drawn into the syringe from the fluid source.
5. The tamper-evident seal is removed from the top of the clear acrylic vial shield (11) exposing the top shielding plug which the seal had secured in place. The plug is now free and is removed by turning the vial shield over adhering to appropriate radiation safety procedures.
6. Once the plug has been removed, the vial shield is returned to its upright position and the septum of the TheraSphere® dose vial (10) is swabbed with alcohol.
7. The 20-gauge needle (9) at the free end of the inlet line (7) is carefully inserted through the center of the TheraSphere® dose vial septum and pushed to the bottom of the vee at the base of the vial.

Assembly of Dose Vial Outlet Set (Table 4 and Diagram 1)

8. The flip-off seal is removed from the empty vial (19).
9. The dispensing pin and filter vent assembly (18) on the free end of the vent line (17) is inserted through the septum of the empty vial.
10. The empty vial is placed in the lead pot used for shipping (20).
11. The 20-gauge needle (12) at the free end of the outlet line (13) is carefully pushed through the septum of the TheraSphere® dose vial until it is just visible below the level of the seal.

System Evacuation (Table 3 and Diagram 1)

12. The red stopcock is switched to the inlet line.
13. The blue stopcock (14) is switched to the vent line.
14. Fluid from the syringe is slowly forced through the inlet line, into the TheraSphere® dose vial, and out through the outlet and vent lines until all air is exhausted from the system and fluid has entered the empty vial.
    NOTE: A low flow rate and gentle tapping of the TheraSphere® dose vial will reduce the possibility of premature introduction of spheres into the outlet line.

15. The outlet needle is pushed half way into the TheraSphere® dose vial. The purpose of this step is to eliminate the possibility of sweeping air that may be trapped near the top of the TheraSphere® dose vial into the catheter.

16. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

17. The red stopcock is switched back to the inlet line.

TheraSphere® Administration (Table 4 and Diagram 1)

18. The patient catheter (16) is attached to the free port (15) on the blue stopcock.

19. The blue stopcock is switched to the catheter.

20. After verifying that both stopcocks are correctly positioned, the fluid in the syringe is expressed at a rate of approximately 1 mL per second. This flow rate will carry the spheres out of the TheraSphere® dose vial, through the outlet line, and into the catheter.

21. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

22. The red stopcock is switched back to the inlet line and another 5 mL of solution is administered as in step 19.

Disassembly (Table 4 and Diagram 1)

23. The blue stopcock is switched to the vent line.

24. The catheter is disconnected from the blue stopcock.

25. The rest of the administration set is disassembled. The empty TheraSphere® dose vial, the dose vial outlet set and the catheter should be stored for decay or disposed of as radioactive waste.

RADIATION DOSIMETRY

The yttrium-90 in TheraSphere® is a constituent of an insoluble matrix thereby limiting irradiation to the immediate vicinity of the spheres. The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of yttrium-90 is 3.85 days; thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

HOW SUPPLIED

TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). The dose is supplied in 0.05 mL of sterile, pyrogen-free water in a vee-bottom vial sealed within a 12 mm clear acrylic vial shield. Each dose is supplied with all the components required for administration, exclusive of items utilized in catheterization. The TheraSphere® dose and Administration Set should be stored at room temperature.

DISTRIBUTION

TheraSphere® is manufactured and distributed by MDS Nordion Inc., Kanata, Ontario, Canada.

BIBLIOGRAPHY

1. Ehrhardt G.J., Day D.E. Therapeutic use of Y-90 microspheres. Int. J. Radiat. Appl. Instrum. Part B. Nucl. Med. Biol. 1987;14:233-242.

2. Mantravadi R.V.P., Spigos D.G., Tan W.S., Felix E.L. Intrarterial yttrium 90 in the treatment of hepatic malignancy. Radiology 1982;142:783-786.

3. Herba M.J., Illescas F.F., Thirlwell M.P., et al. Hepatic malignancies: improved treatment with intraarterial Y-90. Radiology 1988;169:311-314.

4. Houle S., Yip T.K., Shepherd F.A., et al. Hepatocellular carcinoma: pilot trial of treatment with Y-90 microspheres. Radiology 1989;172:857-860.

5. Blanchard R.J.W., Morrow I.M., Sutherland J.B. Treatment of liver tumors with yttrium-90 microspheres alone. J. Can. Assoc. Radiol. 1989;40:206-210.

6. Shepherd F.A., Rotstein L.E., Houle S. ,et al. A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma. Cancer 1992;70:2250-2254.

7. Blanchard R.J.W., Grotenhuis I., LaFave J.W., Perry J.F. Jr. Blood supply to hepatic V2 carcinoma implants as measured by radioactive microspheres. Proc. Soc. Exp. Biol. Med. 1965;118:465-468.

8. Gyves J.W., Ziessman H.A., Ensminger W.D., et al. Definition of hepatic tumor microcirculation by single photon emission computerized tomography (SPECT). J. Nucl. Med. 1984;25:972-977.

9. Meade V.M., Burton M.A., Gray B.N., Self G.W. Distribution of different sized microspheres in experimental hepatic tumors. Eur. J. Cancer Clin. Oncol. 1987;23:37-41.

10. Chuang V.P. Hepatic tumor angiography: a subject review. Radiology 1983;148:633-639.

11. Andrews J.C., Walker S.C., Ackermann R.J., et al. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J. Nucl. Med. 1994;35:1637-1644.

12. Harbert J.C., Ziessman H.A. Therapy with intraarterial microspheres. In: Nuclear Medicine Annual 1987, edited by Freeman L.M., Weissman H.S., Raven Press, New York.

13. Ho S., Lau W.Y., Leung T.W.T., et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur. J. Nucl. Med. 1996;23:947-952.

14. Lau W.Y., Leung T.W.T., Ho S., et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br. J. Can. 1994;70:994-999.

15. Leung T.W., Lau W.Y., Ho S.K., et al. Radiation pneumonitis after selective internal radiation with intraarterial 90-yttrium microspheres for inoperable hepatic tumors. Int. J. Radiat. Oncol. Biol. Phys. 1995;33:919-924.

16. Ho S., Lau W.Y., Leung T.W.T., et al. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur. J. Nucl. Med. 1997;24:293-298.

17. Marn C.S., Andrews J.C., Francis I.R., et al. Hepatic parenchymal changes after intraarterial y-90 therapy: CT findings. Radiology 1993;187:125-128.

18. Wollner I., Knutsen C., Smith P., et al. Effects of hepatic arterial yttrium-90 glass microspheres in dogs. Cancer 1988;61:1336-1344.

19. Zeissman H.A., Thrall J.H., Gyves J.W. et al. Quantitative hepatic arterial perfusion scintigraphy and starch microspheres in cancer chemotherapy. J.Nucl. Med. 1983;24:871-875.

20. Leung W.T., Lau W.Y., Ho S. K., et al. Measuring lung shunting in hepatocellular carcinoma with intrahepatic-arterial technetium-99m macroaggregated albumin. J. Nucl. Med. 1994;35:70-73.

21. Nakamura H., Tanaka M., Oi H. Hepatic embolization from the common hepatic artery using balloon occlusion technique. Am. J. Radiol. 1985;145:115-116.

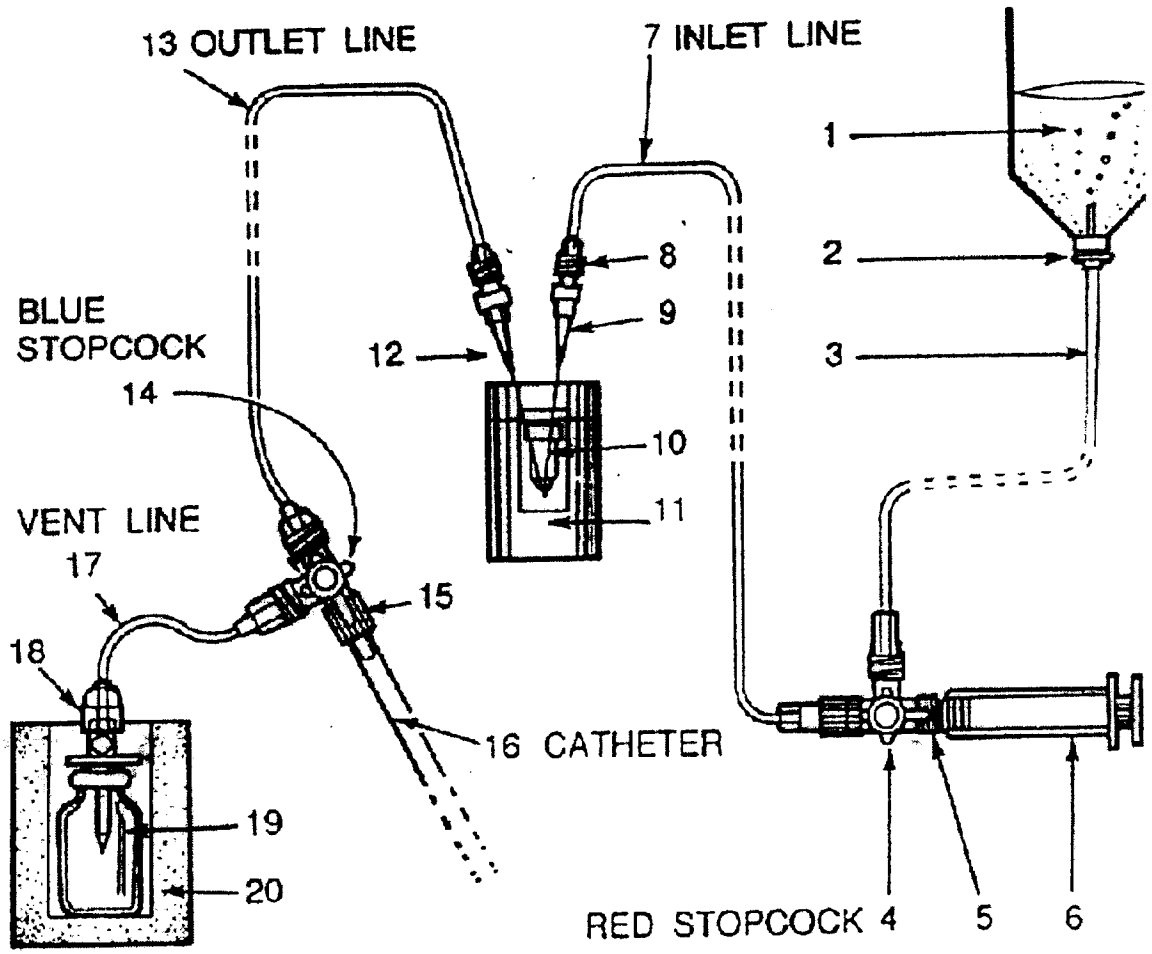
22. Russell J.L. Jr., Carden J.L., Herron H.L. Dosimetry calculations for yttrium-90 used in the treatment of liver cancer. Endocurietherapy/ Hyperthermia Oncology 1988;4:171-186.

23. Synder W.S., Ford M.R., Warner G.G., Watson S.B. "S" absorbed dose per unit cumulated activity for selected radionuclides and organs. NM/MIRD Pamphlet No 11. New York: Society of Nuclear Medicine 1975-1976.

Table 4
TheraSphere® Administration Set Configuration

Drawing Number	Item
1	Fluid source
2	Piercing pin
3	Fluid line
4	Red 3-way stopcock
5	Free port on the red 3-way stopcock
6	5 mL syringe
7	Inlet line
8	Check valve
9	20-gauge needle at the free end of the inlet line
10	TheraSphere® dose vial
11	Acrylic vial shield
12	20 gauge needle at the free end of the outlet line
13	Outlet line
14	Blue 3-way stopcock
15	Free port on the blue stopcock
16	Catheter
17	Vent line
18	Filter vent assembly
19	Sterile empty vial
20	Lead pot

Diagram 1
TheraSphere® Administration Set Configuration



43